Attorney Docket No.: MDSP-P02-180

REMARKS

According to a telephone interview with the Examiner on July 30, 2003, Applicants were informed by the Examiner that the response filed on July 22, 2003 was not received by the Examiner. Applicants hereby resubmit the response filed on July 22, 2003, via facsimile to the Examiner. Applicants submit that the content of the response below is identical to that of the one submitted on July 22, 2003.

Pursuant to an interview with the Examiner on July 15, 2003, Applicants have adopted the Examiner's suggestion to shift election from Group IV claims to Group II claims. Upon entry of the amendments, claims 1, 3, 14, 43-50 constitute the pending claims in the present application. To expedite prosecution, Applicants have canceled claims 2, 4-13, and 15-42. Applicants reserve the right to prosecute claims of identical or similar scope in future applications. Applicants have also added new claims-43-50 to clarify the subject matter claimed. Support for these claims can be found throughout the specification. See, for example, page 23, first full paragraph.

Applicants respectfully request reconsideration in view of the following remarks.

Claim rejections under 35 USC §112, first paragraph

Claims 2, 4, 11, 15-16 are rejected under 35 U.S.C. 112, first paragraph because the specification does not enable any person skilled in the art to practice the invention commensurate with the scope with these claims.

In view of the interview with the Examiner, Applicants have canceled claims 2, 4-13, and 15-42 to expedite prosecution. Applicants reserve the right to prosecute claims of identical or similar scope in future applications.

The Examiner has acknowledged that the specification, especially Example 2, provides the full enabling disclosure to support the anti-IL-11 antibody claims. Thus amended claim 1 and its dependent claims (explicitly supported by at least the first full paragraph of page 23) are all enabled to the full scope.

Particularly, the Office Action asserts that the recitation of "a small molecule" in claim 14 is too broad in that the nature of such a small molecule is left open for determination by the skilled

artisan. In view of the amendment, the nature of the small molecule is no longer left open for determination, and thus this ground of rejection is overcome. For clarification purpose, a single chain antibody scFv may contain a single V_L or V_H domain, each of which is about 110 amino acids in length, or about 12 kDa.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 112, first paragraph.

Claim rejections under 35 USC §112, second paragraph

The Office Action rejects claim 1 under 35 U.S.C. 112, 2nd paragraph, for omitting a positive step for inhibiting the formation of a tertiary complex of IL-11 / IL-11R / gp130, because it is not clear as to what is to be done for achieving inhibition of complex formation. The Office Action alleges that a skilled artisan would not know what is to be administered to achieve the desired result.

While not acquiescing in to the reasoning of the Office Action, Applicants have amended claim 1 to expedite prosecution and to overcome this rejection. Amended claim 1 contains a step of "administering an anti-IL-11 antibody" to achieve the desired result. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. 112, second paragraph, are respectfully requested.

Claim rejections under 35 USC §102(b)

Claims 1-5, 10, 11, 15, 16, 40 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 9619574.

Applicants submit that WO 9619574 is not anticipatory to the amended claims since the cited reference is completely silent about the use of an anti-IL-11 antibody to inhibit the tertiary complex formation in a patient (*in vivo*), not to mention its missing and non-enabling disclosure regarding the opposite effects of IL-11 signaling on osteoclast and osteoblast (and thus bone formation and bone resorption).

Applicants reiterate that, prior to the instant invention, all prior art documents, including Girasole *et al.* (J Clin Invest. 93(4):1516-24, April 1994) as mentioned on page 3 of the instant

specification, fail to teach to suggest that blocking IL-11 would simultaneously inhibit bone loss and stimulate bone formation. Absence of the critical and unexpected discovery of the instant claimed invention (IL-11 has *opposite*, rather than *similar* functions in osteoclast and osteoblast), a skilled artisan simply could not predict whether inhibiting IL-11 signaling *in vivo* (where both osteoclast and osteoblast work against each other in bone remodeling) would actually increase or decrease bone density, or have no / minimal effect at all. For example, the above-mentioned Girasole reference suggests that blocking IL-11 signaling with anti-IL-11 Ab may inhibit osteoclast function *in vitro*. However, Girasole is completely silent about the effect of blocking IL-11 signaling on osteoblast function. It is quite possible that blocking IL-11 can simultaneously block both resorption and bone formation, resulting in a net effect of zero on bone density. Or even worse, blocking IL-11 signaling is more detrimental to osteoblast function (bone formation) than to osteoclast function (bone resorption). In this scenario, blocking IL-11 signaling *in vivo* would actually accelerates bone loss in patients.

In summary, WO 9619574 does not anticipate the claimed invention, reconsideration and withdrawal of rejection under 35 U.S.C. 102(b) is respectfully requested.

Claim rejections under 35 USC §103(a)

Claims 1-5, 10-11, 15-16, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Romas *et al.* (1995) in view of WO 9619574.

Pursuant to MPEP 2143, "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations."

As argued before, Romas suggests that IL-11R is expressed on both osteoclast and osteoblast, and speculates that IL-11 signaling might have a biological function in osteoblasts. However, Romas offers no clue as to what that biological effect might be (especially whether it is stimulatory or inhibitory). In fact, Romas only investigated the role of gp130, the common signal

transducer of a number of cytokines including IL-6, IL-11, OSM, LIF, CT-1, and CNTF (see page 2582, left column, 1st paragraph), in osteoclastogenesis. The data presented only shows that IL-11 can induce osteoclastogenesis *in vitro*, but it cannot rule out the possibility that other cytokines also plays a role in osteoclastogenesis *in vivo*. In fact, it does not even establish that IL-11 plays a major role in osteoclastogenesis *in vivo*. In addition, Romas by no means hinted the unexpected discovery of the instant application that IL-11 signaling is inhibitory (rather than stimulatory) in osteoblast.

WO 96/19574 presents data indicating that soluble IL-11R can promote (rather than inhibit) IL-11 signaling by stimulating proliferation of at least BAF 130-9 cells. Thus, even for the sake of argument, a skilled artisan combines the teaching of Romas and WO 96/19574, the combined reference still does not teach or suggest the claimed invention. In fact, the combined teaching *teaches away* from the claimed invention. This is because a skilled artisan, without knowing any prior example of IL-11 signaling being inhibitory in certain cells such as osteoblasts, would only reasonably assume that IL-11 signaling stimulates cell proliferation. Since IL-11R receptor is present on both osteoclast, which is responsible for bone resorption, and osteoblast, which is responsible for bone formation, the combined teaching is not at all clear as to the possible outcome of IL-11 signaling *in vivo*. Based on the combined teaching, it is even possible, as argued above. that inhibiting IL-11 may depress the function of osteoblast to a greater extent than that of osteoclast, resulting in a net bone loss.

In addition, in view of Nandurkar *et al.* (Blood 90: 2148-2159, 1997, provided as **Exhibit B** in the reply to the previous Office Action), a skilled artisan would further doubt the *in vivo* role of IL-11 signaling in osteogenesis. Accordingly, Applicants submit that at least one of the three requirements for establishing a *prima facie* case of obviousness is not met, reconsideration and withdrawal of rejection under 35 U.S.C. 103(a) are respectfully requested.

Attorney Docket No.: MDSP-P02-180

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Yu Lu, Ph.D.
Reg. No. 50,306

Date: July 30, 2003

Customer No: 28120
Docketing Specialist
Ropes & Gray, LLP
One International Place
Boston, MA 02110
Tel. 617-951-7000
Fax: 617-951-7050